Serum Lactic Dehydrogenase Levels in Various Disease States.* (22353)

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The elevation of serum lactic dehydrogenase (LDH) activity has been observed in association with a variety of diseases. Such elevations have been reported in humans with certain neoplastic diseases(1,2) and in mice with spontaneous, induced and transplanted tumors(3,4). High LDH activity has also been observed in patients with several non-neoplastic disease states, such as diabetic acidosis, myocardial infarction and hepatitis(2), although the number of cases is small and comparative levels of activity between various non-neoplastic and neoplastic diseases have not been specified. It is evident from such preliminary observations that a broad survey of a large variety of disease states is required in order to evaluate properly the clinical significance of changes in serum LDH levels and the usefulness of such determinations as a diagnostic tool. Furthermore, such a survey might suggest possible mechanism for alterations in serum LDH levels. In this report, then, we are presenting the results of such a survey, consisting of 130 individuals free of evidence of clinical disease, and 338 unselected hospital admissions.

Material and method. Clotted venous samples from human subjects were used for this investigation. The blood was allowed to stand at room temperature for no longer than 30 minutes and then centrifuged to separate serum from blood cells. For LDH determination serum samples thus collected were diluted prior to analysis. The micromethod of Strominger and Lowry(5) was used for the determination of level of enzyme activity and the results were recorded as millimoles of substrate oxidized per liter of serum per hour. Storing of uncentrifuged blood samples at 4°C not over one day gave the same result as that obtained with samples kept at room temperature for 30 minutes or less. However, clotted blood samples which remained at room temperature for as long as 60 minutes showed an increase in LDH activity by approximately 25% over those stored at 4°C or at room temperature for no more than 30 minutes. Heparinized and oxalated blood samples also gave LDH values about 40 and 60% higher, respectively, than refrigerated or 30 minute samples. The latter were therefore excluded from the data herein presented. The data have been grouped by organ systems, with subclassification into disease groups, and, except for a graphic presentation of findings in myocardial infarction, are all recorded in Table I. Multiple determinations were made in many cases, but except for those with myocardial infarction, an average was taken in each instance.

Results. (a) Normal controls. LDH was present in all human sera tested. Levels of serum LDH activity were determined in 68 normal females and 62 normal males ranging in age from 10 to 89 years. There was no significant variation with age or sex. The average for all 130 subjects was 15.1 ± 3.01, with a range of variation between 7.5 and 22.7.

(b) Cardiovascular system. There were 87 subjects with various cardiovascular diseases in this survey, and 40 of these were individuals with acute myocardial infarctions. The number of patients whose sera were tested at each time-period following onset of clinical symptoms is recorded at the appropriate points in Fig. 1. In all instances there was a confirming electrocardiographic diagnosis. Some patients were studied for as long as one month after onset of symptoms. The highest serum LDH levels occurred during the first 3 days, with values frequently 3-4 times normal; following this there was a gradual diminution to normal, which was usually observed between the 5th and 6th days after onset. In some instances there was a secondary rise between the 15th and 20th days, which was interpreted as possibly a secondary

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TABLE I. Serum Lactic Dehydrogenase Levels in Normal and Disease States.

Group	No. of cases	Avg	Range of variation
(a) Normal			
Females	68	14.6	7.6– 20.3
Males	62	15.7	9.1– 22.7
(b) Cardiovascular			
Myocardial infarct.*	40		
Hypertensive cardiovascular disease	38	17.5	3.8– 30.8
Mitral stenosis	3	18.0	16.7– 18.8
Subacute bacterial endocarditis	1	27.8	
Pulmonary infarct.	1	22.2	
Gangrene of lower extremity	4	17.7	10.6– 23.0
(c) Central nervous			
Cerebrovascular accident†	18	17.5	8.1– 31.0
Brain tumor	2	18.9	17.8– 19.9
Psychoneurosis	6	14.1	8.4– 16.6
(d) Gastro-intestinal			
Acute infection	13	16.1	10.5– 25.0
Gastric & duodenal ulcer	13	17.4	10.4– 25.9
Carcinoma, pretherapy	8	17.7	13.2– 25.7
post-therapy‡	12	17.1	12.6– 25.3
(e) Urinary			
Acute infection	17	17.0	11.5– 24.0
Chronic nephritis	6	20.8	12.7– 27.5
Carcinoma of kidney	3	18.4	12.5– 22.1
(f) Respiratory			
Acute infection—Lung	10	18.1	10.1– 26.2
—ENT	3	15.1	9.1– 24.3
Chronic " —Lung	3	21.1	17.2– 25.7
—ENT	3	15.9	11.0– 19.9
Carcinoma of lung			
Pretherapy	3	16.1	13.4– 21.4
Post-therapy	4	18.1	13.6– 22.1
Carcinoma of larynx			
Pretherapy	5	20.3	19.8– 21.8
Post-therapy	2	17.2	15.6– 18.7
(g) ♀ genital			
Non-malignant disease	8	13.7	4.8– 18.6
Carcinoma of cervix	4	14.6	9.7– 17.6
(h) Hemopoietic			
Infectious mononucleosis	5	27.2	23.6– 30.2
Thrombocytopenia, post-splenectomy	1	37.1	
Granulocytopenia§	2	14.3	9.4– 17.6
Leukemia, stem cell and myelogenous	4	38.9	24.3– 61.5
Leukemia, chronic lymphocytic	1	13.1	
Lymphoma, pretherapy	3	23.7	21.4– 27.4
post-therapy	3	24.1	13.9– 34.8
(i) Liver, pancreas and biliary tract			
Acute cholecystitis	2	17.1	13.4– 20.7
" infectious hepatitis	1	34.2	
" cholangitis‖	2	35.2	30.2– 40.5
Thorazine hepatitis	1	103.8	
Cirrhosis of liver	7	17.8	14.7– 23.6
Chronic cholecystitis	3	20.2	12.5– 24.4
Carcinoma—metastatic to liver	4	43.2	17.6–106.8
Carcinoma, gallbladder¶	1	40.2	
Ampulla Vater‖	1	36.1	
pancreas**	4	22.8	13.9– 39.4
(j) Breast			
Benign disease	4	15.0	11.3– 18.7
Carcinoma, pretherapy	4	13.8	3.5– 23.3
post-therapy††	8	30.1	5.9–106.8
(k) Miscellaneous			
Rheumatoid arthritis	4	25.1	20.5– 27.8
Fractures	3	15.6	12.0– 19.8
Osteomyelitis	1	19.0	
Diabetes	10	15.4	7.6– 21.4
Myxedema	2	19.7	17.2– 22.2
Hyperthyroidism	1	20.6	
Minor surgery	26	15.6	6.2– 21.4

* See Fig. 1.
† Approximately 40% showed 21.4 to 31.0.
‡ 4 cases had metastatic disease.
§ One case post-splenectomy.
‖ These cases all had obstructive jaundice.
¶ No obstructive jaundice; no metastasis to liver.
** Only 1 case had liver involvement and obstructive jaundice.
†† 5 cases had levels >25, and only 1 had known massive involvement of liver.

attack, but electrocardiographs failed to substantiate such an interpretation. (In addition, one case each of pulmonary infarction and subacute bacterial endocarditis showed slight elevations in serum LDH, but these were possibly associated with small foci of myocardial necrosis.) In 38 cases of hypertensive cardiovascular disease and in 3 with rheumatic heart disease and mitral stenosis values were within normal limits. There were a few cases in the former group with values between 25 and 30, and these may have been associated with small subclinical myocardial infarcts. Surprisingly, 4 subjects with arterial thrombosis and gangrene of the lower extremity also showed LDH values within normal limits.

(c) Nervous system. Neither cerebral infarct, hemorrhage nor primary brain tumor showed average levels of LDH significantly deviating from normal. However, in about 40% of individuals with cerebral infarction and/or hemorrhage LDH levels ranged between 21.4 and 30.

(d) Gastrointestinal tract. It is also evident from the data in this category that acute infectious processes (appendicitis and di-

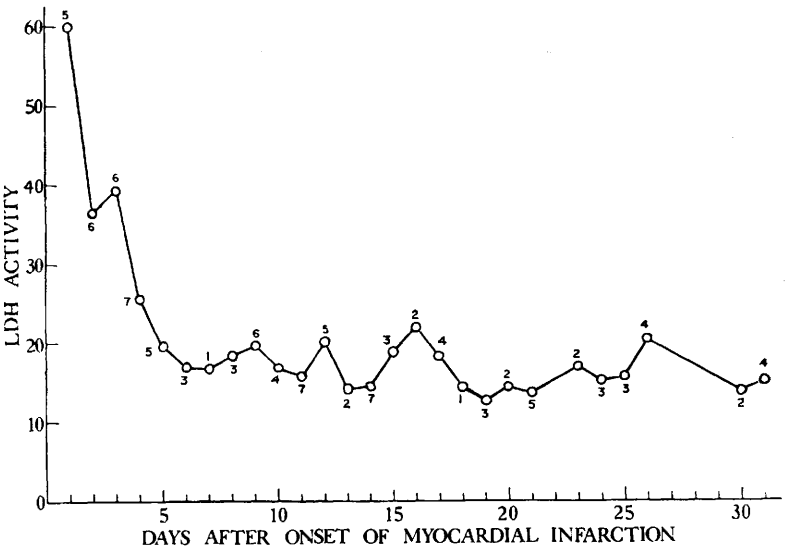

FIG. 1. Serum LDH activity in myocardial infarction.

verticulosis), gastric and duodenal ulcers, some of which were actively bleeding, and carcinoma (stomach, colon and rectum) are not associated with an increase in serum LDH activity. Furthermore, with regard to carcinoma there was no significant difference in LDH activity between patients with the primary tumor, some of whom showed widespread metastases, and those in whom the lesion had been recently resected and in whom no evidence of residual disease was present.

(e) Urinary tract. In 17 patients with acute renal and bladder infections, for the most part secondary to hypertrophy of the prostate, average LDH values were within normal limits, and this was also true of 6 chronic nephritics. There were 3 cases in the latter group with values in excess of 20, but these patients did not show elevated blood urea nitrogen levels, and in several other patients with an elevated blood urea nitrogen LDH values were also within normal limits. Urinary retention and uremia are therefore apparently not associated with elevated serum enzyme levels. In 3 instances of carcinoma of the kidney LDH values were not significantly elevated.

(f) Respiratory system. The results in patients in this group were essentially similar to those with diseases of the gastrointestinal tract. In cases with acute inflammatory disease these were for the most part instances of bronchopneumonia and acute sinusitis, and in the chronic inflammatory group chronic bronchitis and chronic tonsillitis. As regards carcinoma, there was again no significant difference between the pretherapy and posttherapy groups, the latter including patients who had undergone definitive surgery or who were receiving radiation therapy for metastatic disease.

(g) Female genital tract. In this category were included non-malignant diseases of the ovaries, tubes, uterus or cervix (benign tumors and chronic inflammation), as well as 4 cases of epidermoid carcinoma of the cervix. All showed levels of serum LDH activity within the normal range.

(h) Hemopoietic system. In the data shown under the hemopoietic system, infectious mononucleosis consistently gave moderately elevated LDH levels. LDH levels were most strikingly elevated in 4 patients, 2 with stem cell and 2 with myelogenous leukemia, but one patient with chronic lymphatic leukemia showed a normal LDH level. Patients with malignant lymphoma, including Hodgkin's Disease, showed levels comparable to that seen in infectious mononucleosis, with the exception of one case receiving x-ray therapy in whom LDH activity was within nor-

mal limits on several determinations. One patient with splenectomy for thrombocytopenia purpura showed a level about twice average normal; that this was probably not due to splenectomy as such is indicated by the fact that a post-splenectomy patient with granulocytopenia failed to show an increase in LDH activity.

(i) Liver, gallbladder, pancreas and biliary tract. As regards the 25 patients in this category it is evident that cirrhosis of the liver and inflammatory disease of the gallbladder did not produce significant change in LDH levels. However, with lesions that produce obstructive jaundice, such as common duct calculi, Thorazine and malignant tumors, as well as acute infectious hepatitis, LDH levels were elevated to about twice the normal average. Markedly elevated levels were observed in a patient with thorazine hepatitis and one with massive infarction of the liver associated with metastatic carcinoma from the breast.

(j) Breast. In the preoperative state patients with benign lesions and with malignant lesions of the breast without clinical evidence of metastasis showed no significant elevation in serum LDH. However, in 5 of the 8 cases with metastatic disease there was a significant elevation in enzyme activity, and in only one was there massive liver involvement as indicated above.

(k) Miscellaneous. In this category, only the group of 4 arthritic patients gave results deviating from normal. While these were only moderately elevated, they were, however, consistently over 20. One of these was a patient with disseminated lupus.

Discussion. Of the neoplastic diseases investigated, only stem cell and granulocytic leukemia, lymphoma and those involving hepatic metastasis were associated with a consistent elevation of serum LDH activity.

Of the non-neoplastic diseases studied, myocardial infarction, infectious mononucleosis, thrombocytopenia, hepatitis, and obstructive jaundice whether intra or extrahepatic, also gave similar increases in LDH. Since lymphoid, hepatic and cardiac tissues are relatively rich sources of LDH(6), it has been commonly suggested that if necrosis occurs, the enzyme might be released from the damaged tissue into the blood stream, therefore increasing serum LDH. If the tissues involved in disease processes have a low LDH content, one would not expect any significant increase in the total LDH activity. Therefore, they should fall somewhat in the normal range. Furthermore, some neoplastic transformation may depend upon other organs involved as metastatic sites; here, bone appears to be a common metastatic site, since most of these cases showed x-ray evidence of osseous metastasis. It remains for future studies to determine whether tumors of bone, primary or metastatic, are associated with elevated LDH levels.

In the cases of leukemia and infectious mononucleosis and thrombocytopenia the release of the enzyme might be the result of two different causes. First, it could be due to a change in cellular permeability, which possibly results in the secretion of the enzyme from the cells. Secondly, since white blood cells are relatively more fragile in the case of leukemia than normal white cells, the chance of break-down of white cells must be greater and the end result would therefore be the release of enzyme into the blood stream. Other tissues involving neoplasm would be disintegrated more frequently than the normal original tissues, therefore a high normal range level of serum LDH activity was observed in these patients. Other cases with acute infection or leucocytosis of moderate or severe degree showed slight elevation of serum LDH. This elevation might be related to the causes similar to those postulated previously.

The fact that carcinoma of intestine, stomach and kidney, 3 relatively rich sources of LDH(6), gave normal level serum LDH seems to reject the suggestion that serum LDH elevation was due to the release of the enzyme from tissues. While this concept is only plausible, it could be explained as due to some inactivation processes. The enzyme in the gastrointestinal and urinary tracts might be rendered inactive before it entered the blood stream. Furthermore, studies on the rate of urinary excretion of LDH in vari-

ous neoplastic and non-neoplastic diseases may also prove fruitful.

Skeletal muscle and brain tissue of mouse were also pointed out as comparatively rich sources of LDH(6); however, there is no comparable study in human beings. If this finding could be applied to man, then gangrene of the lower extremity should give more striking results than myocardial infarction, and cerebro-vascular accidents should give data comparable to the latter. However, a normal level of serum LDH was noted. This might be explained as follows: The enzyme released from the necrotic tissues in the myocardium have ready access to the flowing blood stream in the cardiac chambers, thus resulting in an elevated serum LDH. Whereas in the leg and brain when occlusion of the major channel of blood occurs, the released enzyme does not have ready access to a blood supply, so the enzyme is destroyed or inactivated before reaching the circulatory system.

Our present studies did not confirm the elevation of serum LDH levels in diabetic acidosis as reported by Wróblewski and LaDue (2). Two of the 10 diabetic patients in the present investigation were in acidosis and the highest value obtained was 21.4. This might be due to the difference of degree in diabetic acidosis.

The mechanism by which serum LDH is increased in association with certain diseases is yet unknown. Experiments relating to the etiology may lead to a clearer understanding of this phenomenon. At present serum LDH determination may be used as a supplementary tool for diagnosing certain neoplastic diseases. It is a good index for myocardial infarction and diseases involving hepatic change.

Summary. The serum lactic dehydrogenase activity of normal human subjects and of patients with various diseases has been studied. Elevated levels were found in such neoplasms as stem cell and granulocytic leukemias, lymphomas, carcinoma of the pancreas and gallbladder, metastasis from carcinoma of the breast, and in metastatic disease of the liver. Increased enzyme activity was also noted in such non-neoplastic diseases as myocardial infarction, infectious mononucleosis, thrombocytopenia, acute infectious hepatitis and obstructive jaundice. Possible mechanisms of such elevation in serum LDH level have been discussed.

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Methemoglobinemia Induced by X-Irradiation.* (22354)

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As a first approximation it may be assumed that X-irradiation produces ion-pairs in aqueous solution as in air and for the same dose that the number of ion-pairs produced per unit weight is the same in solution as in air. A one-roentgen dose of X rays, by definition, produces 2.08×10^9 ion-pairs per 0.001293 g of air and may be considered to produce 1.6×10^{12} ion-pairs per ml of aqueous solution. Also, in aqueous solution containing oxygen there is reason to assume production of oxidant equivalent to 4 univalent atoms per ion-pair. Thus, one roentgen produces the equivalent of 6.4×10^{12} univalent atoms of oxi-

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